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Effect of nadolol in treatment of induced ocular hypertension in rabbits

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Abstract

In glaucoma, as optic neuropathy gradually proceeds unnoticed by the patient, early detection and treatment is of paramount importance in arresting or controlling the progress of damage.

To explore effects of topical nadolol on intraocular pressure (IOP) ocular hypertensive eyes of rabbits.

A group of 36 males of the rabbits were included in this study. Induction of ocular hypertension was achieved by injection of hydroxy propyl methylcellulose in the anterior chamber of rabbits right eye. The present study was designed to evaluate the possible beneficial therapeutic effect. The included rabbits were divided into distilled water group, timolol (0.25% and 0.5%) groups, and nadolol (0.25% and 0.5%). Each of drug eye drops (including distilled water) were instilled into right eyes 3 times/day for 10 days therapeutically. The rabbits had been examined for the IOP, pupil diameter, light reflex, corneal reflex, and conjunctival redness prior to instillation of drugs and along the trial period.

Results: Ocular hypotensive effects of nadolol (0.25%) and (0.5%) eye drops were more efficient than that of distilled water ($P<0.01$). Furthermore, nadolol eye drop was more efficient than timolol eye drop ($0.01>P>0.05$) in its ocular hypotensive effect in both concentrations along the trial period.

In both parts of the present study and regarding each of mean pupil diameter, light reflex, corneal reflex and conjunctival redness, nadolol (0.25% or 0.5%) eye drops had no significant adverse effect ($P > 0.05$).

Conclusions: Nadolol eye drops instilled 3 times / day had an obvious beneficial, safe, and tolerable therapeutic ocular hypotensive effects on hydroxy propyl methyl cellulose - induced ocular hypertension in rabbits.

Keywords: Nadolol; Timolol; Ocular hypertension; Eye drops

1. Introduction

Primary glaucoma which are marked by an increase of intraocular pressure (IOP) are of two main types: primary open angle glaucoma and primary angle closure glaucoma; when optic nerve damage has occurred despite a normal IOP, this is called normal tension glaucoma. Secondary glaucoma refers to any case in which another disease causes or contributes to increase eye pressure, resulting in optic nerve damage and vision loss [1].

In glaucoma, as damage gradually proceeds unnoticed by the patient, early detection and treatment is of paramount importance in arresting or controlling the progress of damage. In recent years, progress in the diagnosis and treatment

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of glaucoma has been remarkable, with numerous new diagnostic and therapeutic aids being introduced in the clinical setting, and the diagnosis and treatment of the disease has become multi-faceted [2].

Medical treatment of glaucoma includes topical β adrenergic antagonists(timolol, levobunolol, carteolol, metipranolol, and betaxolol) [3], topical sympathomimetics (dipivefrin, apraclonidine, and brimonidine) [4], topical cholinergic agonists (pilocarpine, carbachol and ecothiophate iodide) [5], topical carbonic anhydrase inhibitors (dorzolamide and brinzolamid), carbonic anhydrase inhibitors (acetazolamide and methazolamide) [3], topical prostaglandin analogs (latanoprost, travoprost, bimatoprost and unprostone) [5], and osmotic agents (mannitol and glycerin) [6].

Nadolol is a nonselective β-adrenergic antagonist .It produces negative inotropic and chronotropic effects and thus decreases myocardial oxygen consumption [7,8,9] .Nadolol is used in treatment of hypertension, ischemic heart diseases, arrhythmias and congestive heart failure [5,6].

Aim of the study

This study was designed in order to:

- Evaluate the possible therapeutic hypotensive effects of topically applied nadolol on mean IOP values of experimentally induced ocular hypertensive eyes of rabbits.
- Explore the possible local adverse effects of the tested drug in an attempt to assess its safety.

2. Materials and Methods

2.1. Materials

The used materials in the present study are listed below with their sources accordingly:

Table 1 Materials and their sources

Materials	**Source**
Benzalkonium chloride	SDI (supplier)
Nadolol tablets (40 mg)	Emessa Labs /Homs – Syria.
Distillator	Gesellschaft fur Labortech, Nikm. b.h. and Co., type 2016- Germany
Hdroxypropyl methyl cellulose ophthalmic solution (2%) (United states pharmacopoeia)	Focus vision care
Ketamine hydrochloride(50 mg/ml)	HOLDEN MEDICALLelystad the Netherlands
Lidocaine hydrochloride (2%) Solution	Avenzor –Syria
pH. Meter	Friederg/Hessen-Germany
Pupil gauge	Al-Zahrawi Private Hospital
Sartorius balance	Werke–GMBH, type 2842-Germany
Schiotz tonometer	Eichtabelle – Germany
Timolol	Pharmacia Co.- France

2.2. Animal and Housing

A group of 36 adult male of New Zealand rabbits (Oryctologus cuniculus), aged near one year with body weight ranged 1.5-2 kg were included in the study. Animals were kept on fresh trefoil diet, water ad libitum, suitable temperature and normal light.

2.2.1. Induction of ocular hypertension in rabbits

Rabbits had been injected with hydroxpropyl methylcellulose (0.4 ml) of (2% w/v) after proper anesthetization by intramuscular administration of 1ml ketamine hydrochloride. The injection of hydroxpropyl methylcellulose is done by use (27 G *1/2) needle which introduced into anterior chamber and inject 0.4 ml of (2% w/v) hydroxypropyl methyl cellulose to right eye and the left as control , the injection was under sterile condition, and the animals kept in normal light room and suitable temperature and monitored. After 48 hours the IOP increased to (20.1- 23.8 mmHg) and this elevating could persist for 10 days, after that, the IOP start to decrease gradually. The type of induced glaucoma is open angle glaucoma [10, 11, 12].

2.2.2. Preparation of nadolol (0.25%, 0.5 %) eye drops 13:

Table 2 Preparation of nadolol (0.25%, 0.5 %) eye drops

Nadolol	0.25g, 0.5 g
Benzalkonium chloride	(1%) (w / v) 1 ml
Phosphate buffer	to 100 ml

2.2.3. Treatment groups

In the present study, the drugs were administered only to the right eyes of the rabbits whereas the left eyes were administered distilled water.

To evaluate the possible therapeutic hypotensive effects

In this study, the drugs (including distilled water) were administered topically 3 times/day to the right eyes of rabbits only after the ocular hypertension was definitely established, whereas the left eyes received only distilled water.

This part of study was furthermore divided into two subdivisions

2.2.4. Tested agents at (0.25%) concentrations (6 rabbits / group)

- Distilled water (Negative control) group (i.e., Distilled water was administered to both eyes of rabbits).
- Timolol (0.25%) (Positive control) group.
- Nadolol (0.25%) (Tested drug) group.

2.2.5. Tested agents at (0.5%) concentrations (6 rabbits / group)

- Distilled water (Negative control) group (i.e., Distilled water was administered to both eyes of rabbits).
- Timolol (0.5%) (Positive control) group.
- Nadolol (0.5%) (Tested drug) group.

2.3. Tested Parameters

The animals had been examined for the IOP, pupil diameter, light reflex, corneal reflex, and conjunctival redness[14] prior to instillation of drugs and then daily after drugs instillation along the trial period.

2.4. Statistical methods

In this study, the obtained quantitative data were presented as (mean ± S.E.M.) (Standard error of mean). Student paired *t*-test was used for assessing the effectiveness of employed therapy for the right eyes of rabbits in a given group. While student (unpaired) *t*-test for independent data was used to test the significance of the difference between the results of right and left eyes of rabbits in a given group or between the results of the right eyes of rabbits of (any two groups).

The differences were accepted as significant if the calculated value for(t) was equal or greater than its tabulated value at (0.05) level of (P) (i.e. $0.01 < P \leq 0.05$) and highly significant if ($P \leq 0.01$). *Chi*-square (X^2) test was used whenever it was applicable (i.e. for independent qualitative data).

The differences were accepted as significant if ($0.01 < P \leq 0.05$) and highly significant if ($P \leq 0.01$) [15, 16].

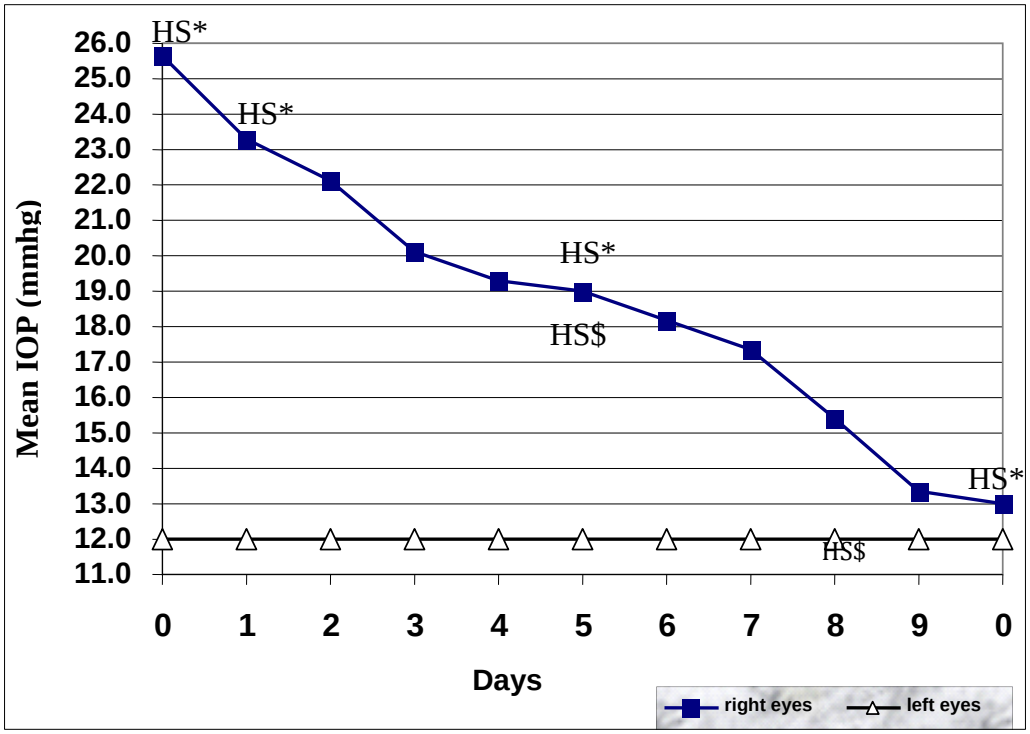
3. Results

3.1. Nadolol (0.25%) group:

Post induction of ocular hypertension the IOP of right eyes was (25.63±0.004 mmHg). Treatment with nadolol (0.25%) eye drop (3 times/day) caused a highly significant decrease in mean IOP from (23.32 ±0.06 mm Hg) to reach (19.01± 0.022 mmHg) within 5 days ($P<0.01$); such decline continued like so for further 5 days of treatment to reach (13.02±0.001 mmHg) by the end of trial period (Figure 1).

Along the trial period, the ocular hypotensive effect of nadolol (0.25%) eye drop was more efficient than that of distilled water ($P<0.01$) and also more efficient than timolol (0.25%) eye drop ($0.01 < P < 0.05$) (Table 1).

Regarding each of mean pupil diameter, light reflex, corneal reflex and conjunctival redness, nadolol (0.25%) eye drops had no significant effect ($P > 0.05$) on them at any time during the trial period.



HS = Highly significant difference ($P \leq 0.01$),* =Compared to corresponding mean IOP values at left eyes, $ = Compared to corresponding mean IOP values of right eyes at first day post induction of ocular hypertension.

Figure 1 Effect of Nadolol (0.25%) eye drops instilled 3 times daily on mean IOP values of rabbit's right eyes (n = 6) with induced ocular hypertension

Table 3 Significance of differences between nadolol (0.25%) and each of timolol (0.25%) and distilled water groups regarding the response of IOP of right eyes of rabbits

	Pre induction	**Post induction of ocular hypertension**			
		Pretreatment	**Post treatment (Day)**		
Group			**1st**	**5th**	**10th**
Distilled Water	NS	NS	HS (N)	HS (N)	HS (N)
Timolol	NS	NS	S (N)	S (N)	S (N)

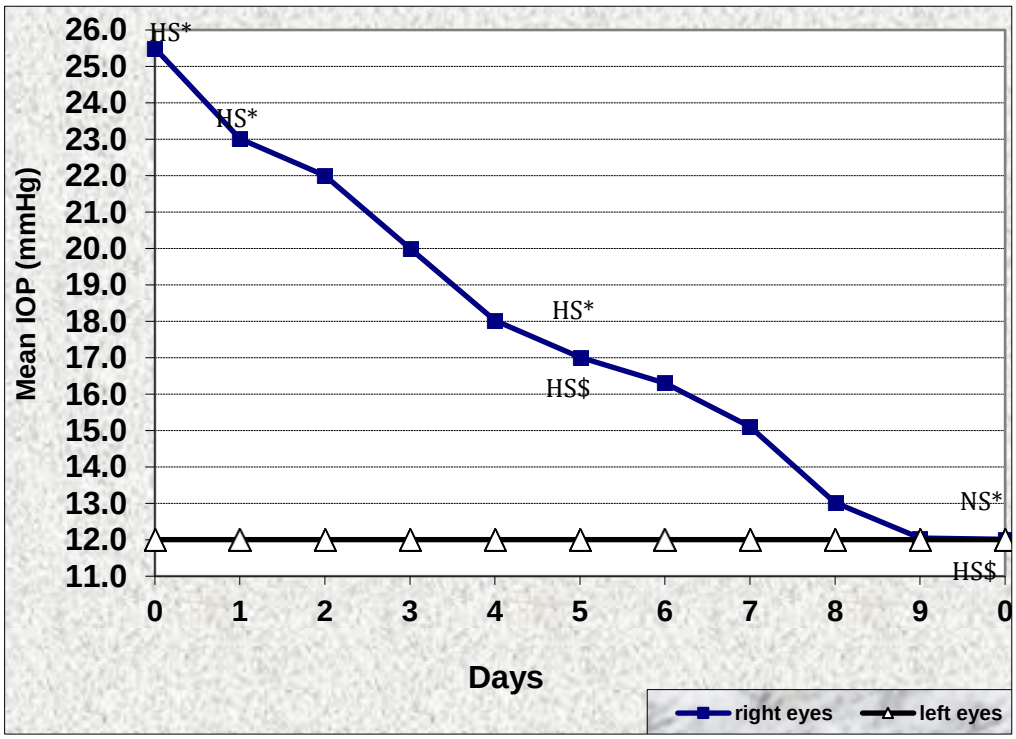
NS = No significant difference ($P>0.05$); HS = Highly significant difference ($P \leq 0.01$); (N) = The lowest value of mean IOP belongs to nadolol group.

3.2. Nadolol (0.5%) group

Post induction of ocular hypertension, the mean IOP of right eyes was (25.5±0.002mmHg). Treatment with nadolol (0.5%) eye drop (3 times/day) highly significant decreased the IOP from (23.01 ± 0.17 mmHg) to reach (17.1 ± 0.01 mmHg) within 5 days (P<0.01); such decline continued like so for further 5 days of treatment to reach (12.01± 0.03 mmHg), by the end of trial period (Figure 2).

During trial period, nadolol (0.5%) eye drop was more efficient than distilled water in its ocular hypotensive effect along the trial period (P<0.01) also was more effective than timolol (0.5%) eye drop (P<0.01) (Table 2).

Compared to distilled water group, nadolol (0.5%) eye drop had no significant effect (P > 0.05) on each of pupil diameter, light reflex, corneal reflex and conjunctival redness at any time during the trial period.



* =Compared to corresponding mean IOP values at left eyes, $ = Compared to corresponding mean IOP values of right eyes at first day post induction of ocular hypertension.

Figure 2 Effect of Nadolol (0.5%) eye drops instilled 3 times daily on mean IOP values of rabbit's right eyes (n = 6) with induced ocular hypertension. NS = No significant difference (P>0.05), HS = Highly significant difference (P ≤ 0.01)

Table 4 Significance of differences between nadolol (0.5%) and each of distilled water and timolol (0.5%) groups regarding the response of IOP of right eyes of rabbits

	Pre induction	**Post induction of ocular hypertension**			
		Pretreatment	**Post treatment (Day)**		
Group			1st	5th	10th
Distilled Water	NS	NS	HS (N)	HS (N)	HS (N)
Timolol	NS	NS	S (N)	NS	S (N)

NS = No significant difference (P>0.05); S = Significant difference (0.01 < P ≤ 0.05); HS = Highly significant difference (P ≤ 0.01); (N) = The lowest value of mean IOP belongs to nadolol group,

4. Discussion

The results of this study, had documented the beneficial therapeutic role of nadolol eye drops at its two tested doses (0.5% and 0.25%) when instilled 3 times/ day for 10 days since each of these concentrations could highly significant ($P < 0.01$) reduced the mean IOP along the trial period in a pattern that was more efficient ($P < 0.01$) than that of distilled water.

And which brought the attention nadolol caused ocular hypotensive effect more than that with timolol. The results and the expected effect of nadolol appeared to be in accordance to what was documented by Osborne *et al.,* (2005) [17] who reported that nadolol potent ocular hypotensive effect.

In agreement to what was found by Sharif *et al.,* (2001) **[18]**, the present study and along the trial period, there was no effect on mean IOP in the contra lateral eye after its topical administration in both ocular normotensive and hypertensive rabbits; this probably indicated that topically applied nadolol exerted its ocular effect locally and not systemically. However**,** these results conflicted with those of Osborne *et al.,* (2005) **[17]** who found the IOP reduction in untreated eye after unilateral topical application of nadolol in rabbits.

Nadolol blocks β adrenergic receptors and thus decreases IOP by reducing aqueous humor production; a mechanism that resembles that of timolol (Kevin and Waschke, 2002**[19]** ; Lacy *et al.,* 2004**[20]**). Furthermore nadolol has duration of action and half life more than that of timolol [9] .

In the present study, when being compared to results of distilled water, nadolol eye drops seemed to be quite tolerable since there was no significant difference ($p>0.05$) between their effects on each of mean pupil diameter, light reflex, corneal reflex and conjunctival redness.

5. Conclusion

Each of nadolol (0.25%) or (0.5%) eye drops instilled 3 times / day had a beneficial, safe, and tolerable ocular hypotensive effects on hydroxy propyl methyl cellulose - induced ocular hypertension in rabbits.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was carried out under care and kindness with animals and the ethical recommendations of the research were taken into account.

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