

The effect of latanoprost and influence of changes in body position on patients with glaucoma and ocular hypertension

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Abstract. – BACKGROUND AND OBJECTIVES: Some patients have an elevation of intraocular pressure (IOP) in the supine position (IOPSP). It has been suggested that topical latanoprost 0.005% (LP) has an attenuating effect on these IOP elevations. The Authors report a simple procedure to evaluate the change in the IOPSP. This paper presents the results of the change in the IOPSP in normals, in patients with ocular hypertension (OH) and in patients with primary open angle glaucoma (POAG). The study also evaluates the effect of the addition of topical LP on those patients with an elevation of their IOPSP.

PATIENTS AND METHODS: Part 1 evaluated the change in the IOPSP in the morning in 40 eyes of normals, 82 eyes in patients with OH and 77 eyes in patients with POAG. The IOP was measured before and after lying in the supine position (SP) for 90 minutes. In part 2 the patients with OH or POAG with an increase in their IOPSP were selected and the test was repeated again after the addition of topical LP.

RESULTS: When compared with normals, the patients with OH and POAG had significantly greater IOPSP increases. The patients with POAG had significantly greater IOPSP increases than did those with OH. The addition of LP partially decreased but did not eliminate the IOP increases in the SP.

CONCLUSIONS: Patients with OH and POAG have a larger increase in their IOPSP than do normals. The addition of topical LP partially decreased but did not totally eliminate these pressure increases.

Key Words:

Intraocular pressure, Intraocular pressure in the supine position, Latanoprost, Ocular hypertension, Primary open angle glaucoma.

Introduction

The relationship between the diurnal variation in the intraocular pressure (IOP) and glaucomatous damage has been studied. Sampaolesi et al¹

examined 100 glaucoma suspects and found that if the IOP varied by more than 2 mmHg, the patients would experience visual field loss. Asrani et al² reported that large fluctuations of the IOP by 10 mmHg or more, were a significant risk factor for glaucomatous progression. In the Advanced Glaucoma Intervention Study (AGIS), the higher the average levels of IOP in glaucomatous patients, the more glaucomatous visual field deterioration³.

The shift from the daytime upright posture to the supine posture at night appears to be associated with the IOP elevations in humans⁴⁻¹¹, as well as in mice¹². This increase may be due to an elevation in the episcleral venous pressure (EVP) that can occur in the supine position (SP)^{4,5,7,8}. There is also a significant linear correlation between the EVP and IOP in patients with normal-tension glaucoma and untreated primary open angle glaucoma (POAG)¹³. Under physiologic conditions the relationship between an elevated EVP and IOP can be estimated by the Goldmann equation which states that the IOP = (aqueous inflow/outflow facility) + elevated EVP¹⁴. According to this formula an elevated EVP uncompensated by a reduction of the aqueous inflow or an increase in the outflow facility will lead to an increase in the IOP. There are disease states such as carotid cavernous fistula that can increase the EVP and cause a secondary glaucoma¹⁵.

The elevated EVP in the SP is thought to be due to an elevated central venous pressure (CVP) that can occur in the SP. Hydrostatic factors in the SP can increase the CVP which then can increase the EVP which in turn can increase the IOP in the SP⁶. The episcleral veins are connected to the central circulation by a valveless system such that increases in the CVP and cephalad shifts in the venous blood caused by changes in the body position will increase the EVP^{16,17}. Elevations of the CVP can also occur in the prone

position during spinal surgery and are associated with elevations of the IOP¹⁸. Artificially increasing and decreasing the CVP by the administration or removal of CO₂ via the respiratory air during general anesthesia causes simultaneous increases and decreases of the IOP⁶. Abrupt elevations of the IOP in a strict-time relationship with the onset of spontaneous or sustained cardiac tachyarrhythmias has also been noted. The Author¹⁹ suggested an elevation of the CVP during the abnormal diastolic cardiac function to explain the IOP elevation.

Due to the possible increase in the supine IOP it would be important to know its distribution in the population. The present study was divided into 2 parts. Part 1 of this study presents a simple procedure to evaluate the change in the IOP in the SP in the office setting in the morning in normals and in patients with ocular hypertension (OH) or POAG. Part 2 of the study evaluates the effect of the addition of topical latanoprost 0.005% (LP) in patients with pressure elevations in the SP.

Patients and Methods

Forty eyes in normals and 159 eyes in patients with either OH or POAG were examined. The eyes were divided into 3 groups. Group 1 were 40 normal eyes, group 2 were 82 eyes with OH and group 3 were 77 eyes with POAG. Glaucoma was defined by computerized visual field changes with the 30.2 program of the Humphrey perimeter. OH was defined as an IOP of 25 mm Hg or more with normal visual fields by Humphrey perimetry. All the patients with OH or POAG were under full topical treatment for their IOP and all had an IOP of 21 mm Hg or less with treatment. Each patient was on the combination of drops that gave the best IOP reduction. Patients who had had previous glaucoma filtration surgery were eliminated. Patients with narrow angles by the Goldmann 3 mirror lens were also excluded. The IOP was measured in both eyes with the Goldmann applanation tonometer in the morning between 8:30 and 9:30 while the patient was sitting at the slit lamp. The patients were then placed on their backs in the SP for 90 minutes with their eyes closed. After 90 minutes in the SP, the patient was again placed in the sitting position at the slit lamp and the IOP was again measured by the same operator with the same Goldmann applanation tonometer. The second

IOP reading was done within 30 seconds from the time that they got up from their SP. The measurement of the IOP in this manner after 90 minutes in the SP will be referred to in this paper as the supine IOP or intraocular pressure in the supine position (IOPSP). The results in this study are reported as a numerical change in millimeters of mercury (mmHg) of the IOP.

The study was divided into 2 parts. In part 1 three groups of eyes were examined. group 1, 40 normal eyes; group 2, 82 eyes with OH; and group 3, 77 eyes with POAG. The patients had their IOP measured in the morning between 8:30 and 9:30 in the sitting position. Their IOPSP was measured 90 minutes later. The results were compared between all 3 groups.

In part 2 the patients with OH and with POAG with an elevation of the IOPSP were selected. The patients were under various topical medications to keep their IOP under 21 mmHg. A comparison was made in their IOPSP first without and then with the addition of a topical prostaglandin, LP. Forty-six eyes (19 eyes with OH and 27 eyes with POAG) were studied as one group. Patients under full topical treatment without LP had their IOP measured in the morning between 8:30 and 9:30 AM and their IOPSP 90 minutes later. LP was then added at bedtime. After 1 week of treatment with the addition of LP, their IOP was repeated in the morning at the same time and their IOPSP 90 minutes later.

Statistical Analysis

The statistical analysis of the results was done with the pooled *t*-test and Mann-Whitney in part 1 and with the *t*-test of individuals and Mann-Whitney in part 2. The Bonferroni correction was used for both parts. The results are expressed as the mean \pm standard deviation (SD). Statistical significance was determined as value $p < 0.05$.

Results

The results of the study are shown in Table I and Figure 1. In group 1, the normals, the IOPSP had an average increase of 0.65 ± 1.87 mmHg, Table I, with a range of -2 to $+6$ mmHg (Figure 1). The normals in Figure 1 had 35 eyes with an increase of 2 mmHg or less and 5 eyes with an increase of 3 mmHg or more of their IOPSP. In group 2, with OH, the IOPSP had an average increase of 2.67 ± 2.75 , Table I, with a range of -2

Table I. The mean and standard \pm deviation (SD) of the intraocular pressure (IOP) reported in mmHg after 90 minutes in the supine position (SP) in part 1 and part 2, without and with prostaglandin (latanoprost) in 46 patients.

Part 1	Means	SD	Part 2	Means	SD
Normals	0.65	1.87	Without latanoprost	6.40	2.90
Ocular hypertension	2.67	2.75	With latanoprost	3.91	2.57
Glaucoma	4.35	3.29			

to +10 mmHg (Figure 1). As seen in the Figure 1, 46 eyes with OH had an increase of 2 mmHg or less and 36 eyes had an increase of 3 mmHg or more of their IOPSP. This increase in the patients with OH when compared with that of the normals was significantly different with a $p < 0.0001$ with the pooled t -test, the Mann Whitney and the Bonferroni correction. In group 3 with POAG, the IOPSP had an average increase of 4.35 ± 3.29 mmHg, Table I, with a range of 0 to +13 mmHg. As seen in Figure 1, 23 eyes with POAG had an increase of 2 mmHg or less and 54 eyes with POAG had an increase of 3 mmHg or more of their IOPSP. This increase in patients with POAG was also significantly different from that of the normals with a $p < 0.0001$ with the pooled t -test, the Mann Whitney and the Bonferroni correction. This increase was also significantly different from that of patients with OH

with a $p = 0.0005$ with the pooled t -test and the Bonferroni correction and with a $p = 0.0008$ with the Mann Whitney and Bonferroni correction. Ten eyes in group 1 and 8 eyes in group 2 had a decrease of -1 or -2 mmHg with their IOPSP. This could represent the small variations that occur when measuring the IOP more than once in the same eye. A decrease in the IOPSP did not occur in group 3, those with POAG.

Part 2 examined the effect of the addition of a LP 0.005% on the IOPSP in the same eye. The results are shown in Table I. Forty-six eyes, 19 with OH and 27 with POAG were studied as one group. The IOPSP in eyes under full treatment without LP increased by an average of 6.4 ± 2.90 mmHg and with the addition of LP the IOPSP increased by an average of 3.91 ± 2.57 mmHg. This difference was significant $p < 0.0001$ with the t -test of individuals, the Mann Whitney and

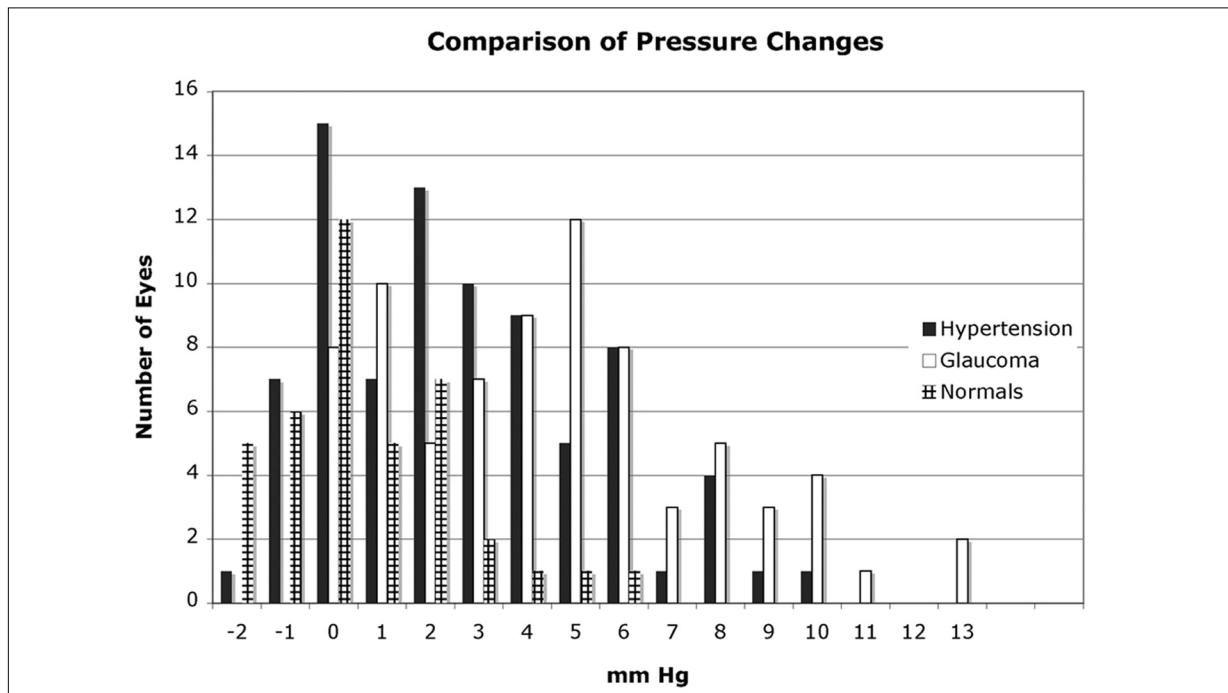


Figure 1. Number of eyes for each change in the intraocular pressure (IOP) in mmHg after 90 minutes in the supine position (SP) Part 1. in the 3 groups: normals and patients with ocular hypertension (OH) or glaucoma (POAG).

the Bonferroni correction. The addition of LP to the other drops lowered the IOP. The average IOP in the sitting position in the morning under full treatment without LP was 19.6 mmHg and 15.4 mmHg after the addition of LP for 1 week. The difference was significant with a $p < 0.0001$ with the t-test of individuals and with the Bonferroni correction, and a $p = 0.0006$ with the Mann-Whitney and Bonferroni correction. There was a tendency for the LP to lower the pressure increase of the IOPSP but it did not eliminate it. Although the addition of LP only partly decreased the pressure increase, the eyes with LP had lower IOPs to begin with so that the final IOPs after 90 minutes in the SP were still lower with the addition of LP than without.

Discussion

The evaluation of pressure spikes is an important factor to consider in patients with OH or POAG. Previous studies have shown that diurnal variations in the IOP are associated with glaucomatous damage^{1,2}. The higher the average IOP in glaucomatous patients, the more likely glaucomatous field damage³. Elevations in IOPSP have been identified during the day^{4,7,10-11}, as well as at night^{8,9}. In this study the normals, group 1, did have an average IOPSP elevation of 0.65 mmHg with spikes to 6 mmHg. This increase is smaller than that recently reported of 2.4 ± 2.12 mmHg¹¹. The average elevation of the IOPSP in group 2 with OH was 2.67 mmHg and in group 3 with POAG was 4.35 mmHg. However, the IOPSP had spikes to 10 mmHg in group 2 and to 13 mmHg in group 3. The difference in the elevations between group 2 and 3 was significant. This difference could be expected since the patients in group 3 had POAG while those in group 2 had OH. These increases of the IOPSP may help to explain the reason for the progression of glaucoma in some patients with apparently good IOP control during routine office exams but this needs further studying. These increases in the IOPSP may also help to explain why some patients with OH progress to POAG and others don't. Ophthalmologists are accustomed to measuring the IOP only in the sitting position in the office setting in their patients with OH and POAG. IOP measurements in the SP during the day or night are not routinely done. This kind of information could, however, prove to be useful

since most patients spent approximately a third of their 24 hour day in the SP when they sleep. Those with pressure spikes probably need to be treated more aggressive. Moreover, a recent study²⁰ found a 2-fold increase in the IOP in normal eyes after 5 minutes during Sirsasana (headstand posture) in 75 yoga practitioners.

We wanted to present a simple test to detect and evaluate the IOPSP in our patients. The above described method between 8:30 and 9:30 AM in the office setting with the use of a bed and the Goldmann applanation tonometer at the slit lamp was found to be easy to perform. It is now used routinely for all of our patients with OH or POAG. An arbitrary time of 90 minutes in the SP was selected. It is possible that the increase in the IOPSP could be evaluated in a shorter time, 15 or 30 minutes for example, but this was beyond the scope of the study. Patients with narrow angles were excluded. We measured the IOP in the sitting position with the Goldmann applanation tonometer within 30 seconds from the time the patient got up from the SP. Preliminary measurements found that IOP elevations in the SP were maintained for 2 minutes but at 5 minutes began to drop. To be within the 2 minute time limit, we arbitrarily selected a limit of 30 sec which was easy to perform in the office. It is possible that the time limit could be longer but this is matter of further study.

The major factor for the IOP increase in the SP is thought to be due to an increase in the EVP due to an augmented CVP in the SP. This investigation was designed to study this change during the day. One would expect an elevation of the IOP at night in the supine due to the same mechanism but this needs to be studied. The rate of aqueous humor flow at night is only about half of the daytime value²¹, and this could influence IOP elevations at night in the SP.

In part 2 LP was topically added to a group of eyes with previously recognised elevations in their IOPSP. This was done because previous studies showed that topical LP had a sustained IOP-lowering effect during the nocturnal period when compared with that of topical timolol 0.5%²²⁻²⁸. This suggests that a topical prostaglandin, such as LP, could have an attenuating effect on IOP elevations at night in the SP. In this study the addition of LP did not eliminate the pressure elevations in the supine position. The addition of LP lowered the pressure elevations in the SP from an average increase of 6.4 mmHg without LP to an average increase of 3.9

mmHg with the addition of LP. LP lowers the IOP by increasing aqueous humor outflow presumably through the uveoscleral outflow pathway²⁹. LP is not known to influence the CVP in the SP. Since the elevation of the CVP in the SP is thought to be the cause of the IOP elevations and since LP is not known to influence the CVP, one would not expect an elimination of IOP increases with the addition of LP. In those patients with an elevation of their IOPSP, the addition of a prostaglandin should still be considered. While LP only had a partial effect on lowering the increase of the IOPSP, it still had an average attenuating effect on the IOP elevation of 2.5 mmHg. Furthermore, the addition of LP lowered the initial average IOP from 19.6 to 15.4 mmHg. It is possible that LP lowers the initial IOP enough and decreases the increase of the IOPSP enough, that the final IOP in the SP is more tolerable for an eye.

The present method for measuring the IOPSP was easy to perform and well tolerated by the patients. Ophthalmologists can easily do it as long as they have a bed near their Goldmann tonometer. Further research is necessary to correlate these increases with nocturnal increases, glaucomatous progression and the conversion of OH to POAG. Psychophysical and electrophysiological testing can be useful for early detection of patients at risk of developing POAG³⁰. These tests could also be useful in following the patients with pressure spikes in the SP.

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