Efficacy of one drop of 2% pilocarpine to reverse the intraocular pressure peak at 6:00 a.m. in early glaucoma

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Funding: This study was supported by an educational grant from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil through the Programa Institucional de Bolsas de Iniciação Científica (PIBIC).³
Proprietary and/or financial interest: None

ABSTRACT

Purpose: To assess the efficacy of one drop of 2% pilocarpine (2% Pi) at night to reverse the intraocular pressure (IOP) peak at 6:00 a.m. in the daily curve of intraocular pressure (DCPo) of pre-perimetric open-angle glaucoma.

Methods: We retrospectively analyzed the charts of patients with early glaucoma. We compared the IOP values at 6:00 a.m. in the same eye of two DCPos. In the first DCPo, the patients were without medication, and in the second they were using one drop of 2% Pi between 10:00 and 10:30 p.m. for at least six months. Each DCPo had five IOP measurements taken at 9:00 a.m., 12:00, 6:00 and 10:00 p.m. (Goldmann applation tonometer) and in the morning of the following day at 06:00 a.m. (Perkins tonometer) in a supine position in bed and in darkness before the patient had stood up. The pre-perimetric glaucoma patients, without medication, presented an IOP peak at 6:00 a.m. in the DCPo. This peak represents a difference ≥7 mmHg between the IOP value at 6:00 a.m. and that lesser IOP at any other time in the DCPo. An IOP peak reversion at 6:00 a.m. under 2% Pi occurred when the difference between the IOP at 6:00 a.m. and the lesser IOP was ≤5 mmHg in the DCPo. Patients with secondary glaucoma were excluded. We set the significance level at 5% (P<0.05).

Results: Sixty-one eyes of 35 patients with an average age of 56.1 years were included. Under 2% Pi the IOP peak at 6:00 a.m. reversed significantly (Χ²=7.96; P=0.005) in 44 (72.1%) eyes. The mean IOP dropped from 22.1±2.3 mmHg in the DCPo without medication to 16.8±2.7 mmHg in the DCPo under 2% Pi (t=7.9; P<0.001).

Conclusion: One drop of 2% Pi at night is effective to reverse the IOP peak at 6:00 a.m. in pre-perimetric glaucoma.

Key words: Glaucoma, Intraocular pressure, pilocarpine, efficacy.

INTRODUCTION

Primary open-angle glaucoma (POAG) is one of the main causes of irreversible blindness in the world.¹ It is mostly asymptomatic, discovered unexpectedly in routine intraocular pressure (IOP) measurements and/or in optic disc or visual field exams.¹,² There is much evidence that an elevated IOP is the principal risk factor for optic nerve damage that results in visual field loss.²

The Advanced Glaucoma Intervention Study (AGIS) demonstrated that long-term IOP fluctuation is associated with a progression of visual field loss in patients with low mean IOPs, but not in patients with high mean IOPs.² The daily intraocular pressure curve (DCPo) is considered the most reliable method for the evaluation of IOP fluctuations in early glaucoma diagnosis, as well as in its treatment.³

Pilocarpine was one of the first drugs to be used in the treatment of POAG.⁴ It is a direct muscarinic cholinergic drug which increases the drainage of aqueous humor through Schlemm’s canal. It is normally used three to four times a day. After the introduction of new drugs, the use of pilocarpine decreased due to its side effects (miosis, ciliary muscle spasm, myopia, cataract, etc), although it is still one of the cheapest drugs available for the treatment of POAG.⁵ Studies demonstrate that aqueous humor production follows a circadian rhythm.⁶-⁸ In normal patients, the aqueous humor production decreases about 50% at night.⁹¹⁰ As pilocarpine increases aqueous humor drainage, it is theoretically the most indicated drug for night use in order to reverse the IOP peak at 6:00 a.m. in pre-perimetric glaucoma patients.

This study aims to assess the efficacy of one drop of 2% pilocarpine (2% Pi) at night to reverse the IOP peak at 6:00 a.m. in the DCPo of glaucoma patients without visual field loss (pre-perimetric glaucoma).
METHODS

We retrospectively analyzed patients’ charts from the Glaucoma Service of the São Geraldo Hospital. The study was approved by the Ethics Committee of the Federal University of Minas Gerais, and adhered to the principles enshrined in the Declaration of Helsinki. Informed consent was obtained from all patients. We registered the patients’ demographic data.

We compared two DCPos from the same patients. In the first DCPo, the patients were without medication, and in the second the patients were using one drop of 2% Pi between 10:00 and 10:30 p.m. for at least six months.

The use of only one drop of 2% Pi between 10:00 and 10:30 p.m. was an endeavor to reverse the IOP peak at 6:00 a.m. that these patients presented in the absence of medication. This IOP peak at 6:00 a.m. represents a difference equal to or greater than 7 mmHg between the IOP measurement at 6:00 a.m. and the lesser IOP measurement taken at 9:00 a.m. or 12:00, or 6:00 or 10:00 p.m. in the DCPo. An IOP peak at 6:00 a.m. under 2% Pi was reversed when the difference between the IOP at 6:00 a.m. and the lesser IOP measurement in the DCPo was ≤ 5 mmHg which is the normal diurnal IOP fluctuation.11–14 Each DCPo consisted of five IOP measurements taken at 9:00 a.m., 12:00, 6:00 and 10:00 p.m. (Goldmann applanation tonometer) and in the morning of the following day at 06:00 a.m. (Perkins tonometer) in a supine position in bed and in darkness before the patient had stood up. The Perkins tonometer is essentially a portable Goldmann applanation tonometer that can be used with the patient in either upright or supine position.13

We included open-angle glaucoma patients with a normal visual field (pre-perimetric glaucoma) done with an Octopus 1–2–3 perimeter that, without medication, presented an IOP peak at 6:00 a.m. in the DCPo. We have only selected eyes with pre-perimetric glaucoma due to its initial glaucoma stage, which can possibly be treated effectively with a minimum dose of an antiglaucomatous drug.

Besides the normal visual field, the diagnostic criteria for pre-perimetric glaucoma were based on at least two of the following findings: 1. IOP values from 19 to 25 mmHg in isolated tonometry; 2. vertical cup disc ratio ≥ 0.7 with localized optic disc notching and thinning; 3. asymmetry of the cup disc ratio ≥ 0.3.

Due to the IOP peak at 6:00 a.m. the patients also presented an abnormal DCPo. This was demonstrated by an abnormal mean IOP (IOPm) and/or an abnormal standard deviation (SD) when compared with the normal IOPm and SD from healthy age-matched individuals previously studied in our Service by one of the authors15 (Table 1).

RESULTS

Sixty-one eyes of 35 patients (27 women and 8 men) were included. The patients’ average age was 56.1 years. Seven (20%) patients were white; 21 (60%) were fodermic (Brazilian mulattos) and seven (20%) were black. Nine eyes were excluded for not presenting an IOP peak at 6:00 a.m. in the DCPo without medication. All sixty-one eyes presented an IOP peak at 6:00 a.m. without medication and a normal visual field. After using 2% Pi between 10:00 and 10:30 p.m., the IOP peak at 6:00 a.m. was reversed in 44 (72.1%) eyes with a statistically significant difference (X² = 7.96; P = 0.005). In 17 (27.9%) eyes, the IOP peak at 6:00 a.m. was not reversed.

The IOPm at 6:00 a.m. was 22.1 ± 2.3 mmHg in the first DCPo. After using 2% Pi, a high percentage (72.1%) of eyes had a reversal of the IOP peak at 6:00 a.m. There was a statistically significant reduction in the IOPm at 6:00 a.m. in the DCPo without medication and after using 2% pilocarpine in eyes with pre-perimetric glaucoma.

DISCUSSION

It is widely recognized that the IOP varies throughout twenty-four hours.16,17 The IOP reduction is the only goal in the treatment of glaucoma.2

From the best of our knowledge, this study is the first to evaluate the efficacy of one drop of 2% Pi used between 10:00 and 10:30 p.m. to reverse the IOP peak at 6:00 a.m. in the DCPo. After using 2% Pi, a high percentage (72.1%) of eyes had a reversal of the IOP peak at 6:00 a.m. There was a statistically significant reduction in the IOPm (t = 7.9; P < 0.001). Therefore, in agreement with Sirbat, our results demonstrate that, despite well-known adverse effects, pilocarpine remains a useful medication.5

Table 1. Superior normal limits of mean intraocular pressure (IOPm + 2 SD) and of standard deviation (SD + 2 SD) from the DCPo of normal eyes previously studied by Calixto15

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>n</th>
<th>IOPm</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 25</td>
<td>24</td>
<td>14.62</td>
<td>2.28</td>
</tr>
<tr>
<td>26 to 35</td>
<td>22</td>
<td>15.93</td>
<td>2.28</td>
</tr>
<tr>
<td>36 to 45</td>
<td>20</td>
<td>16.66</td>
<td>2.63</td>
</tr>
<tr>
<td>46 to 58</td>
<td>20</td>
<td>16.92</td>
<td>2.22</td>
</tr>
</tbody>
</table>

DCPo, daily curve of intraocular pressure; IOPm, mean intraocular pressure; SD, standard deviation; n, number of eyes.
In this paper, 2% Pi was useful to reverse the IOP peak at 6:00 a.m. in a high percentage of eyes. As a consequence of the IOP peak reversion at 6:00 a.m. the 24-hour IOP control was obtained in those eyes since no IOPs changes occurred at 9:00 a.m. and at 12:00, 6:00 and 10:00 p.m.. On the other hand, in some eyes (27.9%), as happens with other antiglaucomatous drugs, 2% Pi was unable to reverse the IOP peak at 6:00 a.m. (Table 2).

The findings of this paper were not comparable with prior studies because we did not find any similar study in literature.

One question that may arise is why one drop of 2% Pi at night was chosen to reverse the IOP peak at 6:00 a.m. The principal answer is the fact that the patients included in this paper only presented an IOP peak at 6:00 a.m. without medication in the DCPo. We have chosen one drop of 2% Pi to reverse the IOP peak at 6:00 a.m. instead of a selective or non-selective beta-blocker, a \( \alpha_2 \)-agonist, a topical carbonic anhydrase inhibitor or a prostaglandin analog for the following reasons:

1. Two percent Pi is the only topical antiglaucomatous drug that truly reduces the IOP by increasing the outflow facility of aqueous humor via Schlemm’s canal. As the pathogenetic mechanism of glaucoma is an increased resistance to aqueous humor drainage via Schlemm’s canal, the instillation of one 2% Pi drop should be considered the most rational choice to reverse the IOP peak at 6:00 a.m.

2. A selective or non-selective beta-blocker, a \( \alpha_2 \)-agonist and a topical carbonic anhydrase inhibitor diminish the IOP by reducing the aqueous humor production. As aqueous humor production is already physiologically reduced about 50% at night, these drugs should not be the most recommended only to reverse the IOP peak at 6:00 a.m. In addition, the reduction of aqueous humor production by the above-mentioned drugs could well cause a long-term reduction of the permeability of the external wall of the trabecular meshwork due to a reduced volume of aqueous humor in circulation.

3. The prostaglandin analogs reduce the IOP by increasing the aqueous humor outflow through the uveoscleral via. The patients of this study only had an IOP peak at 6:00 a.m. and no elevated IOP during the day nor visual field loss (pre-perimetric glaucoma). Therefore, the prostaglandin analogs would not be so indicated. In general, these drugs are remarkably efficient in reducing the IOP and can be prescribed for patients with an elevated IOP and advanced glaucoma. Furthermore, one drop of prostaglandin analogs is very expensive in comparison with one drop of 2% Pi, which is one of the cheapest antiglaucomatous drugs.

4. It is well known that miosis, ciliary muscle spasm and myopia are common side effects caused by pilocarpine when it is used three to four times a day. However, when pilocarpine is instilled only once at night in the effort to reverse the IOP peak at 6:00 a.m., those side effects are not present. In some patients, the presence of a light miosis might occur the following day; however, this does not cause any problem due to the patients’ age in this study. In this series, no patients complained the following day after using one drop of 2% Pi between 10:00 and 10:30 p.m.

Despite the limitations placed by the small sample, this paper demonstrates the benefit of using one drop of 2% Pi between 10:00 and 10:30 p.m. to reverse the IOP peak at 6:00 a.m. It reduces the IOP peak at 6:00 a.m. in the majority of eyes from pre-perimetric glaucoma patients. Consequently, the IOP fluctuation reduction might prevent the risk of glaucoma progression.

**CONCLUSION**

One drop of 2% Pi at night is highly likely to be effective to reverse the IOP peak at 6:00 a.m. in pre-perimetric glaucoma patients.

**REFERENCES**

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