*Original Article*

# Efficacy of 2% Pilocarpine on Intraocular Pressure (IOP) Lowering Effect in Uncontrolled Primary Open Angle Glaucoma (POAG) Patients with Maximal Medication

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**Objective**: To evaluate the additive intraocular pressure (IOP) lowering effect of 2% pilocarpine eye drops in medically uncontrollable primary open angle glaucoma (POAG) patients.

**Materials and Methods**: The present study was a retrospective study on POAG patients whose IOP were unable to be controlled with topical hypotensive agents who refused glaucoma surgery. Pilocarpine eye drops (2%) was considered as an additive treatment option. The main measurement was IOP at baseline and after adding pilocarpine eye drops (2%) at 1-, 3- and 6-months. Statistical analysis was described in terms of mean ± standard deviation (SD). Comparisons of numerical variables were done using paired t-test. A p-values of less than 0.05 was considered statistically significant.

**Results**: Thirty-one eyes in 19 patients with open angle glaucoma were enrolled. The mean age of the patients was 62 years. Thirteen patients were male. The mean number of baseline medications was 4.0±0.3. IOP was reduced from 25.0±2.1 mmHg at baseline to 19.0±1.98 mmHg after one month, to 19.0±1.86 mmHg after three months, and to 19.0±1.73 mmHg after six months, which was statistically significant ($p<0.001$).

**Conclusion**: Pilocarpine eye drops (2%), when used additional with others topical hypotensive agents, was effective for IOP lowering. Patients in the present study reported reduced IOP. The efficacy of pilocarpine eye drops (2%) made it a viable treatment option, particularly for the uncontrollable open angle glaucoma patient who refused glaucoma surgery.

**Keywords**: Pilocarpine eye drops (2%); Intraocular pressure (IOP); Medically uncontrollable; POAG

Received 15 September 2021 | Revised 7 April 2022 | Accepted 20 April 2022

**J Med Assoc Thai 2022;105(7):606-9**

**Website:** http://www.jmatonline.com

Glaucoma is the second leading cause of blindness worldwide[1]. Increase intraocular pressure (IOP) is considered to be the most important risk factor and the only one that can be modified. Lowering of IOP is known to delay disease progression for patients diagnosed with glaucoma[2,3]. Five broad drug classes are commonly used to lower IOP in patients with glaucoma, prostaglandin analogues (PGAs), beta-blockers, alpha2-agonists, carbonic anhydrase inhibitors (CAI), and cholinergic agents. When patients cannot tolerate these medications or fail medical therapy, lowering of IOP must be achieved with incisional glaucoma surgery[4].

Pilocarpine, a cholinergic agent, has been commonly used in the past to lower the IOP. This agent is highly effective with over a century of experience. In primary open angle glaucoma (POAG), pilocarpine contracts the ciliary muscle, increasing the outflow of aqueous humor to reduces IOP. Pilocarpine eye drops (2%) should be administered three to four times per day and is usually used in combination with other anti-glaucoma drugs. Pilocarpine is seldom used today as an ocular hypotensive agent because it irritates the ocular surface and more effective medications are readily available[5].

Some patients refused filtering surgery for lowering IOP even if the eye pressure could not be controlled with the maximal of four classes of hypotensive agents. Therefore, these patients were prescribed pilocarpine eye drops (2%) as an additive hypotensive agent combined with other anti-glaucoma drugs for lowering IOP.

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**How to cite this article:**

Phruancharoen C. Efficacy of 2% Pilocarpine on Intraocular Pressure (IOP) Lowering Effect in Uncontrolled Primary Open Angle Glaucoma (POAG) Patients with Maximal Medication. J Med Assoc Thai 2022;105:606-9.

**DOI**: 10.35755/jmedassocthai.2022.07.13335

The purpose of the present study was to evaluate the additive IOP lowering effects of pilocarpine eye drops (2%) in medically uncontrollable POAG patients who refused glaucoma surgery.

## Materials and Methods

The present study was a retrospective review of patient medical records at Naresuan University Hospital. The charts of all patients who were diagnosed as uncontrolled open-angle glaucoma in at least one eye between 2014 and 2021 were reviewed. Pilocarpine eye drops (2%) was administered four times daily in addition to their previous anti-glaucoma agents. Age, gender, best corrected visual acuity (BCVA) (logMAR), Cup to disc ratio, Visual field mean deviation (dB), and numbers of medication were recorded. The major measurement was IOP at baseline and after adding pilocarpine eye drops (2%) at 1-, 3-, and 6-months. The presence of ocular and systemic side effect were recorded.

The inclusion criteria were the patients diagnosed as unilateral or bilateral uncontrolled POAG and were followed up for at least six months after adding pilocarpine eye drops (2%). The exclusion criteria were the primary angle closure glaucoma (PACG), the secondary glaucoma including uveitic glaucoma, neovascular glaucoma, and phacomorphic glaucoma, and had received previous glaucoma surgery. All patients underwent a complete ophthalmic examination, including a BCVA test, slit lamp examination, gonioscopy, Goldmann applanation tonometry, fundoscopy, and 24-2 Humphrey visual fields. The patients unable to tolerate ocular and systemic side effects of pilocarpine eye drop (2%) were excluded. The medically uncontrollable POAG was defined as IOP more than 21 mmHg with maximal anti-glaucoma medication except cholinergic agent, open angle, and glaucomatous optic neuropathy. All continuous variables were analyzed through mean and standard deviation, while paired t-test was used to compare IOP. A p-value of less than 0.05 was statistically significant. The present study was approved by the Institutional Review Board of Naresuan University (IRB No. P3-0127/2564).

## Results

Nineteen patients with 31 eyes were included in the present study. The mean age of the patients was 62 years. A majority of the patients were male. Mean IOP (±SD) was 25.0±2.10 mmHg at baseline. The mean number of baseline topical anti-glaucoma medications was 4.0±0.3 (Table 1). The base line medications are shown in Table 2.

**Table 1.** Demographic data (n=31 eyes)

| Variable | Mean±SD |
|---|---|
| Age (years) | 62.0±5.46 |
| Male; n (%) | 13 (68) |
| Best corrected visual acuity (logMAR) | 0.30±0.23 |
| Mean base line IOP (mmHg) | 25.0±2.10 |
| Mean number of base line anti-glaucoma drugs | 4.00±0.3 |
| Cup to disc ratio | 0.70±0.12 |
| Visual field mean deviation (dB) | –10.59±3.29 |

IOP=intraocular pressure; SD=standard deviation

**Table 2.** Medical treatment at baseline

| Type of pre-treatment | Number of eyes |
|---|---|
| B+A+C+P | 28 |
| B+C+P | 1 |
| B+A+P | 2 |

A=alpha2-agonist; B=beta blocker; C=carbonic anhydrase inhibitor; P=prostaglandin analogue

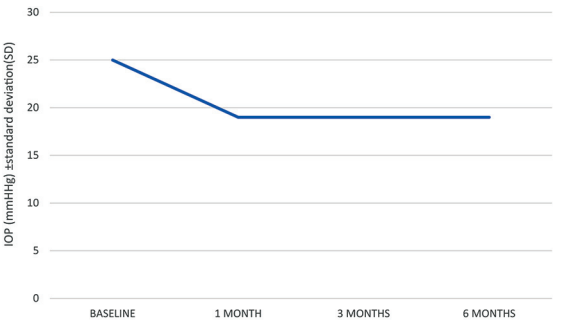


**Figure 1.** Mean intraocular pressure (IOP) ± standard deviation (SD) for all patients (p<0.001).

One month after adding pilocarpine eye drops (2%), mean IOP was reduced to 19±1.98 mmHg, after three months to 19.0±1.86 mmHg, and after six months to 19.0±1.73 mmHg (Figure 1). At 1-, 3- and 6-months, the overall IOP values were significantly lower than the baseline values (p<0.001) (Table 3).

The side effect observed was in only one patient out of 19 patients in the present study and was not serious, which was temporary irritation of the eye. Three of nineteen patients were excluded because they could not tolerate the side effect of pilocarpine eye drops (2%). A major reason was blurred vision and headache.

## Discussion

In patients with glaucoma, five broad medication

**Table 3.** Intraocular pressure and intraocular pressure reduction from base line at each follow-up visit

| | IOP; mean±SD | IOP reduction; mean±SD | p-value |
|---|---|---|---|
| Baseline | 25.0±2.10 | | |
| 1-month | 19.0±1.98 | 7.0±1.58 | <0.001 |
| 3-month | 19.0±1.86 | 7.0±1.68 | <0.001 |
| 6-month | 19.0±1.73 | 6.5±1.73 | <0.001 |

IOP=intraocular pressure; SD=standard deviation

p<0.05 was defined as statistically significant

types are routinely utilized to reduce IOP. The alpha2-agonist, beta-blocker, and CAI can all achieve IOP reduction primarily through reduction in aqueous humor production. The PGAs achieve IOP reduction primarily through an increase in aqueous outflow through the uveoscleral pathway[6]. Pilocarpines achieve IOP through increasing the outflow of aqueous humor by stimulating ciliary muscle contraction. Due to frequent doses and side effects, pilocarpine is not commonly used as a first hypotensive agent. It was recommended as second, or third line drugs[7]. Despite target IOP reduction therapy, glaucoma patients frequently require additional treatment to keep their target IOP. The appropriate additional therapy is not as well defined, and it can differ from one clinician to another[8,9].

In the present study, the authors demonstrated the IOP effects of adjunctive pilocarpine therapy in medically uncontrolled open-angle glaucoma patients who refused glaucoma surgery because of their own reasons. Pilocarpine eye drops (2%) was considered the additive treatment options four times per day. This combination of topical hypotensive agents had only been researched in a limited way. The present study shows marked reduced IOP from a baseline of 25.0±2.1 mmHg to 19.0±1.73 mmHg at 6-months, p<0.001. Similarly, Leonard et al reported the addition of pilocarpine could significantly lower IOP throughout the diurnal and nocturnal periods, in patients that were on PGA monotherapy. During the diurnal period, pilocarpine significantly reduced IOP from a baseline of 18.2±0.5 mmHg on PGA monotherapy to 17.1±0.4 mmHg, p<0.01. During the nocturnal period from 21.1±0.7 to 20.0±0.6 mmHg, p<0.01[10].

Evidence demonstrates that addition of pilocarpine to the treatment regimens of patients already taking other hypotensive agents is an effective combination of medications for the treatment of elevated IOP. Toris et al explained the additivity of latanoprost and pilocarpine. Aqueous humor dynamics were assessed in ocular hypertension. They showed that latanoprost increased uveoscleral outflow while pilocarpine increased outflow facility. Additionally, pilocarpine did not block or attenuate the uveoscleral outflow effect of latanoprost. The result was greater IOP reduction when these drugs were used in combination than when either drug was used alone[11]. Beta blockers also had partially additive effect with pilocarpine[12,13]. Pilocarpine may also be used effectively in combination with carbonic anhydrate inhibitors. This addictive effect also is effective for alpha2-agonist[14].

The decrease in IOP caused by long-term pilocarpine treatment is dependent on the pilocarpine concentration utilized. Based on the small number of reports of adverse effects in children with childhood glaucoma, concentrations of up to 2% may be safe[15]. It is commercially available in Thailand. Systemic toxicity of pilocarpine is rare with the usual doses of pilocarpine used in the chronic management of glaucoma. The danger comes with large doses given within brief period of time[16]. Robin et al reported 10% to 15% of patients treated with pilocarpine or the combination therapy were terminated from further participation because of typical pilocarpine side effects such as blurred vision and headache[17]. Similarly, three of seventeen patients in the present study could not tolerate the side effect of pilocarpine eye drops (2%) and were excluded. A major reason is blurred vision and headache. Fewer than 10% of all included patients experienced mild symptoms as temporary irritation of the eye.

The present study was limited by the small number of patients and the retrospective design, which has unavoidable bias. A prospective study including a larger sample size and longer follow-up is needed.

## Conclusion

These results suggest that pilocarpine may be effective and safe in the glaucoma patients with poorly controlled IOP on multiple hypotensive agent therapy. Pilocarpine had an additive effect when used as a fourth or fifth drug for patients who need further IOP reduction, particularly for the glaucoma patient who refused glaucoma surgery.

## What is already known on this topic?

Pilocarpine has an additive IOP lowering effect to other hypotensive agents. Due to side effects and new developed medications, pilocarpine was not as widely used as in the past.

## What this study adds?

This study reported the good additive IOP lowering effect of pilocarpine in medically uncontrollable POAG patients. It may be an additional drug for POAG patients who need further IOP reduction.

## Conflicts of interest

The authors declare no conflict of interest.

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